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Pooled exposure–response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study

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Abstract

Objectives: Silica is one of the most common occupational exposures worldwide. In 1997 the International Agency for Research on Cancer (IARC) classified inhaled crystalline silica as a human carcinogen (group 1), but acknowledged limitations in the epidemiologic data, including inconsistencies across studies and the lack of extensive exposure–response data. We have conducted a pooled exposure–response analysis of 10 silica-exposed cohorts to investigate lung cancer.
Methods: The pooled cohort included 65,980 workers (44,160 miners, 21,820 nominees), and 1072 lung cancer deaths (663 miners, 409 nonminers). Follow-up has been extended for five of these cohorts beyond published data. Quantitative exposure estimates by job and calendar time were adopted, modified, or developed to permit common analyses by respirable silica (mg/m^3) across cohorts.
Results: The log of cumulative exposure, with a 15-year lag, was a strong predictor of lung cancer ($p = 0.0001$), with consistency across studies (test for heterogeneity, $p = 0.34$). Results for the log of cumulative exposure were consistent between underground mines and other facilities. Categorical analyses by quintile of cumulative exposure resulted in a monotonic trend with odds ratios of 1.0, 1.0, 1.3, 1.5, 1.6. Analyses using a spline curve also showed a monotonic increase in risk with increasing exposure. The estimated excess lifetime risk (through age 75) of lung cancer for a worker exposed from age 20 to 65 at 0.1 mg/m^3 respirable crystalline silica (the permissible level in many countries) was 1.1–1.7%, above background risks of 3–6%.
Conclusions: Our results support the decision by the IARC to classify inhaled silica in occupational settings as a carcinogen, and suggest that the current exposure limits in many countries may be inadequate. These data represent the first quantitative exposure–response analysis and risk assessment for silica using data from multiple studies.

Introduction

In October 1996 the International Agency for Research on Cancer (IARC) convened a Working Group to evaluate the evidence regarding the potential carcinogenicity of silica. The Working Group concluded that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (group 1)" [1]. The classification for crystalline silica was reached largely as a result of some very supportive findings from individual studies. However, there were some studies that did not demonstrate lung cancer excesses, and the IARC conclusion remains somewhat controversial [2]. Exposure–response trends were not always consistent in studies in which such analyses had been done. Furthermore, exposure

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measures differed between studies, making it impossible to produce a meta-analysis of exposure–response estimation across all studies.

In view of the importance of quantitative exposure–response analysis for causal inference and occupational exposure standard-setting, we have conducted a pooled analysis of lung cancer in relation to quantitative crystalline silica exposure among 10 occupational cohorts. Vital status follow-up has been extended beyond published data for five cohorts. New quantitative estimates of exposure have been developed for three cohorts, and modified or extended for four others. Pooled analyses have several advantages over typical meta-analyses based on published reports [3, 4]. These advantages include construction of common exposure measures and a uniform approach to data analysis that may reconcile differences in interpretation among studies due to differences in analytic methods.

Materials and methods

Materials

We reviewed the literature to identify all cohorts which had quantitative exposure data, or for which quantitative exposure data could potentially be developed. We identified 13 cohorts, 10 of which we included in the pooled analysis. Three cohorts were excluded due to confidentiality issues (Dutch ceramic workers [5]), data unavailability (one cohort of South African gold miners [6]), or incompatibility of data (English case–control study of pottery workers [7]). This last study was not comparable to our pooled nested case–control data because of different case–control matching criteria; while we did not include this study directly, we did consider its results indirectly.

Studies of silica-exposed workers in coal mines and foundries were also excluded. Silica in coal mines is not considered equivalent to silica in other settings, due to the low silica content of the dust (5%) and because of different surface properties which appear to affect biological activity. Silica particles in many coal mines are coated with clay and may be less toxic than uncoated silica [8, 9]. The IARC did not consider studies of lung cancer among coal miners in its evaluation of silica carcinogenicity, and coal dust was evaluated separately from silica [1]. We have followed this precedent, and have not included one large study of British coal miners with good silica exposure data [10]. Finally, we did not attempt to include studies of workers exposed in foundries, as these exposures are usually confounded with exposure to polycyclic aromatic hydrocarbons (PAHs), some of which are lung carcinogens.

Of the 10 studies included in this analysis, five have been updated for mortality since their latest publications (US gold miners [11], Finnish granite workers [12], Chinese pottery workers [13], Chinese tungsten miners [13], Chinese tin miners [13]); one cohort was newly developed in parallel to this pooled analysis (US industrial sand [14]). In addition, new quantitative exposure measures by job and calendar time have been developed or modified for several studies (Australian gold miners [15], US granite workers [16], US industrial sand workers [14], Finnish granite workers [12], Chinese pottery workers [13], Chinese tungsten miners [13], Chinese tin miners [13]). The 10 cohorts include five cohorts of underground miners. The pooled cohort size consists of 65,980 workers (44,160 miners, 21,820 nonminers), among whom 1072 lung cancer (lung, trachea, bronchus) deaths occurred (663 miners, 409 nonminers). The three Chinese studies include nonexposed workers (32% of the Chinese workers); in other cohorts all workers were exposed. Table 1 lists the relevant studies, with references.

A separate unpublished paper (Mannetje *et al*., Reconstruction of existing exposure data for the application to 10 silica-exposed cohorts for a pooled analysis, submitted, 2001) describes the exposure data in all studies in more detail and describes the process of creating a common exposure metric (mg/m^3 respirable silica) across studies. Below we provide a brief description of each of the 10 cohorts included in the present analysis.

1. US diatomaceous earth workers. The mortality of this cohort by level of cumulative exposure has been described by Checkoway *et al*. [17] and Rice *et al*. [18], while the development of estimated exposure levels (mg/m^3 respirable silica) has been described by Seixas *et al*. [19]. No additional effort was needed to use this cohort in the pooled analysis.

2. South African gold miners. Mortality by level of cumulative exposure (mg/m^3 dust, 30% silica) has been described by Hnizdo *et al*. [20, 21]. Only minor work was needed to adapt this cohort to the pooled analysis. Exposure to radon in these mines was considered relatively low, with the average working level (1.3×10^5 MeV of alpha energy per liter of air [22]) estimated to be 0.4 [20]. By comparison, US uranium miners with heavy exposure to radon averaged 16 working levels [22]. Nonetheless, as most miners in this cohort worked for long periods of time (median 24 years), this level of radon could have led to a

Table 1. Description of the 10 studies

Studies (nonmine/mine)[a]	Reference	No. dead	No. of workers	End of follow-up[c]	Median cumulative exposure to respirable silica (mg/m^3-years)	Median duration of exposure (years)	Median average exposure to respiratory silica (mg/m^3)
US diatomaceous (nonmine)	Checkoway *et al.* 1997 [17]	749	2342	1994	1.05	4.3	0.18
Finnish granite (nonmine)	Koskela *et al.* 1993 [12]	418	1026	1993	4.63	9.2	0.59
US granite (nonmine)	Costello *et al.* 1988 [16]	1762	5408	1982	0.71	18.0	0.05
US industrial sand (nonmine)	Steenland *et al.* 2000 [14]	860	4027	1996	0.13	3.7	0.04
China pottery[b] (nonmine)	Chen *et al.* 1992 [13]	1592	9017	1994	6.07	26.4	0.22
China tin[b] (mine)	Chen *et al.* 1992 [13]	956	7858	1994	5.27	25.4	0.19
China tungsten[b] (mine)	Chen *et al.* 1992 [13]	4549	28,481	1994	8.56	25.9	0.32
South Africa gold (mine)	Hnizdo *et al.* 1997 [20]	1009	2260	1986	4.23	23.8	0.19
US gold (mine)	Steenland *et al.* 1993 [11]	1925	3348	1996	0.23	5.4	0.05
Australia gold (mine)	De Klerk *et al.* 1998 [15]	1351	2213	1993	11.37	26.8	0.43
Total		15171	65,980		4.27	23.9	0.19

[a] All studies are cohort studies.

[b] 50%, 40%, and 24% of Chinese pottery, tin, and tungsten cohorts were in largely unexposed jobs, and were assigned a minimum level of 0.01 mg/m^3 silica; medians for exposure and duration are here reported for exposed only.

[c] Follow-up for three Chinese cohorts extended 5 years, for Finnish cohort 4 years, for US gold miner cohort 6 years, beyond original publication. Follow-up began at time of first exposure (after fulfilling any minimum required length of exposure), or in 19.40, whichever was later.

cumulative radon exposure of approximately 80 WLM over a lifetime (24 years $\times$ 0.4 WL $\times$ 12 months $\times$ 5/7 days/week), which in US uranium miners would lead to a relative risk of approximately 1.2–1.3 [23]. Some miners would of course have had longer and higher exposures. Given the possibility of confounding by radon in this cohort, we analyzed the data with and without this cohort in the pooled analysis.

3. US gold miners. Mortality and morbidity findings by level of cumulative exposure in the total cohort have been described previously by Steenland *et al.* [11, 24], and mortality for part of this cohort was studied previously by McDonald *et al.* [25]. Quantitative job-specific estimates of exposure (mg/m^3 respirable silica) over time were available for this cohort, as were detailed work histories. No extra work was required to adapt this cohort for the pooled analysis. The original authors updated this cohort for mortality by 6 years (though 1996) for the pooled analysis. Exposure to radon in these mines was relatively low, with measurements in the 1970s ranging from 0 to 0.17 working levels.

4. US industrial sand workers. Mortality findings from this cohort have recently been reported [14] (another study of US industrial sand workers with considerable overlap with this one has also recently been published [26], with findings similar to the study used here). Previous work has documented high silicosis risks in this industry [27, 28]. The cohort used here consisted of 4027 workers, all of whom had at least 1 week of employment and adequate detailed work history. A NIOSH industrial hygienist developed quantitative job-specific estimates of exposure over time based on extensive data from the 1970s and 1980s collected at all 18 plants in the study, as well as more limited data collected at a number of US industrial sand plants in the 1940s [29].

5. Australian gold miners. Western Australian gold miners have been analyzed by de Klerk and Must [15]. Eighty-four miners without complete work history or with no follow-up after a medical survey (which was required to enter the cohort) were deleted, leading to a cohort of 2213 miners. De Klerk (personal communication 1999) developed job- and time-specific exposure

estimates (mg/m^3 respirable silica), based on industrial hygiene data collected since 1925 [30]. Conversion of early konimeter count data was made to gravimetric data which have been collected since 1977. The authors reported that radon levels in these mines were negligible.

6. US (Vermont) granite workers. This cohort was originally published by Costello and Graham [16]. Complete work histories were available for this cohort. Attfield (personal communication, 1999) developed job-specific quantitative exposures over time for this cohort using data on granite workers' exposure published earlier [31–33]. Average predust control and postdust control exposures were calculated for 22 job classifications, which were then matched to the job titles in the work history of the cohort. Follow-up for the pooled analysis was not extended beyond the original 1982, although some additional deaths prior to that data were identified and added to the file.

7, 8, 9. Chinese pottery workers, tin miners, and tungsten miners. Mortality data for this multi-industry cohort were published by Chen *et al*. [13]. Work history data in the cohort included dates of first and last employment for the job in which the worker had been exposed to the highest dust exposure for at least 1 year. Quantitative job-specific exposure estimates over time in terms of total dust were developed by Dosemeci *et al*. [34] in conjunction with a nested case–control study [35]. We converted total dust measurements (mg/m^3) to estimated respirable silica based on side-by-side sampling of traditional Chinese total dust sampling and modern sampling of respirable silica, which was conducted in all Chinese facilities in these three industries in the late 1980s [36]. The original job-specific exposure estimates in the 1992 nested case–control study were generalized and used to estimate job-specific exposure for all cohort members. Work history data were reviewed and updated by the original authors, and follow-up was extended from 1989 to 1994 (further updating of the work history data is ongoing, and should enable future analyses to rely on more complete work history). The original Chinese data [13] also included iron and copper mines with low levels of silica, but these mines have not been included in the latest update of work history or mortality follow-up and are not included here. Thirty-two percent of the Chinese workers were either surface miners or pottery workers who were not directly exposed. These workers were assigned a minimal level of exposure (0.01 mg/m^3) to silica.

Radon, arsenic, and mixtures of polycyclic aromatic hydrocarbons (PAHs) were potential confounders for lung cancer in these cohorts (PAHs only for the potteries). However, radon exposure was uncommon and prior analyses [35] suggested that neither radon nor PAHs were major confounders, although arsenic could have confounded results in the tin mines. As data on these potentially confounding exposures were not available in other cohorts, preventing a uniform treatment in the pooled analysis, and as quantitative job-specific exposure over time had not been developed for them, we did not attempt to adjust for these other exposures in our pooled analyses. Instead, we conducted some analyses excluding the three Chinese cohorts altogether, to determine the effect of their omission on silica/lung cancer exposure–response trends.

10. Finnish granite workers. Koskela *et al*. [12, 37] have published cohort and nested case–control analyses of this cohort. These authors extended estimation of exposure over time for each worker from the nested case–control study to all cohort members for the purpose of this pooled analysis. In addition mortality follow-up was extended from 1985 to 1994.

Methods

Some external analyses (SMR analyses) [38] were conducted using national mortality rates as a comparison with mortality in our exposed population, when such rates were available. Rates for the US were available from NIOSH [38]. Rates for Finland and Australia were available from the IARC [39]. Rates for China were available from other investigators (Ziqing Zhuang, personal communication, 2000). No rates were available for South Africa. Analyses were restricted to underlying cause of death. Follow-up began at date of first exposure or cohort entry, or after any minimum required length of employment was fulfilled (some studies had such requirements), or at the time rates began, whichever date was later. Rates were available from 1940 onwards for the US, and from 1960 onwards for other countries.

The focus of the analysis was on internal exposure–response analyses. The pooled analyses were conducted via nested case–control analyses using conditional logistic regression (in which the likelihood is equivalent to Cox regression) (SAS, PROC PHREG [40]).

In the nested case–control analyses a risk set for each case was assembled composed of those who had survived to an age at least as great as the case, and which was matched for race (relevant only for US studies), sex, date of birth (within 5 years), and study to the index case. Matching by study was done to account for different background male lung cancer rates across studies, which ranged from 32/100,000 in China

to 58/100,000 for the US. Matching by study also tends to stratify on study-specific characteristics, such as the quality of exposure data. After the risk set for each case as indicated above, 100 controls were randomly chosen from each risk set to be compared to the index case, sufficient to assure good statistical precision and approximating the point estimate which would have been obtained using full risk sets [41]. Given the matching on confounders, exposure–response models included only an exposure variable, or an exposure variable and interaction terms between study and exposure.

Categorical analyses of cumulative exposure and average exposure (cumulative exposure/duration) were conducted by quintiles, with cutpoints chosen from the distribution of exposure among the cases. For analyses of exposure as a continuous variable, the principal analyses used log linear models ($\log RR = \beta X$), where X was either cumulative exposure (mg/m^3-days), the (natural) log of cumulative exposure, or average exposure. We also considered lags of 0, 5, 10, 15, and 20 years. Lags discount any recent exposure, under the assumption in cancer studies that a period of latency is required before cancer can develop. Constants of 1.0 and 0.005 were added to cumulative exposure or average exposure, respectively, when taking the logs, to avoid taking the logarithm of 0 in lagged analyses. We also used a log-linear restricted cubic spline [42] model (five knots at 5%, 25%, 50%, 75%, 95%) to assess further the shape of the exposure–response trend in a relatively unconstrained model, as well as a piece-wise linear model in which two separate linear slopes were allowed. Finally, we also considered a linear relative risk model ($RR = 1 + \beta X$).

We tested for heterogeneity by mine *vs.* nonmine via an interaction term between mining and exposure. Overall heterogeneity between studies was assessed by comparing the model likelihood of a model with a main exposure effect and 10 study–exposure interaction terms with the likelihood of a model with only the main exposure effect. In addition, individual heterogeneity between any one study and the remaining studies was assessed by single study–exposure interaction terms.

We also conducted some exposure–response analyses of silicosis mortality (underlying cause ICD9 code 502, $n = 794$) as a method of assessing the validity of our exposure estimates; positive exposure–response trends should be evident for silicosis if our exposure estimates were accurate. These analyses were conducted with nested case–control methods analogous to those described above. A more detailed analysis of silicosis mortality will be the subject of a separate paper.

Excess lifetime cumulative risk of lung cancer death was estimated using the results of the models and converting rates to risk. We assumed an exposure at 0.10 mg/m^3 from age 20 to age 65, and a lifetime through age 75. The 0.10 mg/m^3 level is as the permissible occupational level for quartz (the most common form of silica) in many countries, including Canada, France, Belgium, Italy, Norway, Sweden, Denmark, Argentina, Portugal, and South Africa [1]. In the US the permissible level depends on the percent of silica (quartz) in respirable dust, but is 0.10 mg/m^3 when the respirable dust is 100% quartz. We also considered lower levels of exposure, 0.02 and 0.01 mg/m^3. Adjustment for background mortality rates (competing risks) was done via the method proposed by Gail [43]. We calculated excess risk for males for three countries: the US, Finland, and China. We used country-specific and age-specific background rates for lung cancer and all causes for males for the early 1990s. Country-specific lung cancer rates were taken from the IARC [39], while background all-cause death rates for the US, Finland, and China were available either from NIOSH (US), the WHO (Finland), or other investigators (China, personal communication, Ziqing Zhuang, 2000).

Results

Table 1 provides descriptive information on each cohort as well as the median average exposure level and the median cumulative exposure level. Table 2 provides SMRs for lung cancer for nine of the 10 cohorts.

The analysis of silicosis mortality (underlying cause, ICD9 code 502) resulted in odds ratios, by quintile of cumulative exposure of the cases, of 1.0, 3.1 (2.5–4.0), 4.6 (3.6–5.9), 4.5 (3.5–5.8), and 4.8 (3.7–6.2). These results suggest our job-exposure matrix was reasonably successful in estimating exposure. The lack of a strictly monotonic trend by cumulative exposure could be due to several factors besides inaccuracies in the job exposure matrix. These include restriction of analyses to underlying cause (silicosis in the US frequently appears as a contributing cause) and differing medical practices between countries in identifying silicosis as the underlying cause of death. In contrast to results for cumulative exposure, analysis of silicosis mortality by quintile of duration of exposure did not show a clear trend (odds ratios 1.0, 1.3 (1.0–1.6), 1.8 (1.4–2.3), 1.4 (1.1–1.7), 1.2 (0.89–1.5), indicating the importance of incorporating level of exposure in the exposure metric.

Table 3 lists coefficients for exposure–response trends for lung cancer by study, using three different exposure metrics in the usual log-linear model ($\log RR = \beta X$); cumulative exposure lagged 15 years, the log of cumulative exposure lagged 15 years, and average exposure

Table 2. SMRs for lung cancer in the study cohorts[a]

Study	SMR lung, 95% CI	SRR, *vs* non-exposed[b]	Lung cancer deaths[c]
US diatomaceous [17]	1.3 (1.0–1.6)		77
Finnish granite [12]	1.4 (1.0–2.0)		38
US granite [16]	1.2 (1.0–1.3)		124
US industrial sand [14]	1.6 (1.2–1.9)		85
China pottery [13]	1.1 (0.84–1.4)	2.8 (1.6–4.8)	68
China tin [13]	2.1 (1.7–2.6)	1.5 (0.98–2.4)	97
China tungsten [13]	0.63 (0.53–0.75)	0.92 (0.63–1.3)	135
South Africa gold [20]	n.a.[a]		77
US gold [11]	1.2 (1.0–1.4)		156
Australia gold [15]	1.8 (1.5–2.1)		135
Total	1.2 (1.1–1.3)		992

[a] Referent rates for US studies are US rates developed by NIOSH. For Finland and Australia the rates come from the World Health Organization. For China the rates were supplied by Dr Chen [13]. No comparison rates were available for South Africa. For Chinese cohorts the SMRs are for the exposed workers only, *vs* the national population. SMR for the combined group excludes South Africa.
[b] 50%, 40%, and 24% of Chinese pottery, tin, and tungsten cohorts were unexposed.
[c] Lung cancers among exposed workers only; total includes the South Africa lung cancers.

Table 3. Exposure–response coefficients for each of the 10 studies

Study	Coefficient cumulative exposure, 15-year lag[a] (se)	Coefficient log cumulative exposure, 15-year lag (se)	Coefficient average exposure[b] (se)
US diatomaceous [17]	0.0500 (0.0219)	0.0887 (0.0538)	0.1459 (0.2883)
South Africa gold [20]	0.2099 (0.0909)	0.6665 (0.3359)	7.789 (2.761)
US gold [11]	0.0058 (0.1453)	0.0388 (0.0775)	0.0181 (0.0252)
Australia gold [15]	0.0161 (0.0120)	0.1937 (0.1154)	0.5539 (0.3139)
US granite [16]	0.0146 (0.0285)	0.1121 (0.0496)	0.3824 (0.9417)
Finnish granite [12]	0.0080 (0.0102)	0.0489 (0.0698)	0.3523 (0.2588)
US industrial sand [14]	0.1774 (0.1153)	0.0312 (0.0568)	4.432 (1.590)
China tungsten [13]	0.0095 (0.0022)	0.0297 (0.0257)	0.1724 (0.0573)
Chine pottery [13]	0.0037 (0.0164)	0.0764 (0.0362)	0.2436 (0.3333)
China tin [13]	0.0358 (0.0078)	0.0784 (0.0341)	0.9417 (0.2357)
Pooled	0.0105 (0.0022)	0.062 (0.015)	0.047 (0.023)

[a] Cumulative exposure units are mg/m^3-years.
[b] Average exposure units are mg/m^3.

(cumulative exposure/duration). Table 3 shows that there is considerable heterogeneity of results by study, especially for cumulative exposure (lag 15 years) and average exposure. The results for these metrics for the pooled data are shown at the bottom of Table 3. These pooled results should be considered with caution in the light of the considerable heterogeneity shown across the 10 studies, especially for cumulative exposure and average exposure.

We are not aware of any methodological differences between studies which would explain the observed pattern of heterogeneity. The South African cohort had the highest exposure–response. As noted earlier (see Methods), the level of radon in the South Africa mines was not negligible and could have acted as a confounder in that study. The US gold cohort had the lowest exposure–response, without any obvious explanation. Others have hypothesized that physical differences in silica exposure between cohorts (*e.g.* freshness of particle cleavage, degree of coating with dust [8, 9]) may be a partial explanation of observed differences in results, but we have no information on how these factors may have differed from one cohort to another in our study.

Table 4 shows the pooled results in more detail for a several log-linear models, for both continuous and categorical exposure variables. The categorical data by quintile of cumulative exposure showed a monotonically increasing trend. The models in Table 4 using cumulative exposure and average exposure displayed substantial heterogeneity in exposure–response between studies, while the models using the log of cumulative exposure and the log of cumulative exposure lagged 15 years did

Table 4. Combined analyses, nested case–control; coefficients (se) and odds ratio (95% CI) for cumulative exposure to respirable silica

Exposure variable	Combined studies: coefficient (se)	Combined studies: odds ratios (95% CI)
Cumulative exposure[a] Heterogeneity[b]	0.008 (0.002) (model likelihood 17.3, 1 d.f.) $p = 0.008$	
Cumulative exposure, 15-year lag Heterogeneity[b]	0.010 (0.002) (model likelihood 21.4, 1 d.f.) $p = 0.02$	
Log cumulative exposure[a] Heterogeneity[b]	0.067 (0.016) (model likelihood 19.2, 1 d.f.) $p = 0.08$	
Log cumulative exposure, 15-year lag[a] Heterogeneity[b]	0.062 (0.015) (model likelihood 18.8, 1 d.f.) $p = 0.34$	
Average exposure[d] Heterogeneity[b]	0.047 (0.022) (model likelihood 4.4, 1 d.f.) $p < 0.0001$	
Categorical odds ratio[c]: cumulative exposure		1.0, 1.0 (0.85–1.3), 1.3 (1.1–1.7), 1.5 (1.2–1.9), 1.6 (1.3–2.1) (model likelihood 21.0, 4 d.f.)
Categorical odds ratios[c]: cumulative exposure lagged 15 years		1.0, 1.0 (0.83–1.3), 1.3 (1.0–1.6), 1.5 (1.2–1.8), 1.5 (1.2–1.9) (model likelihood 17.3, 4 d.f.)
Categorical odds ratios[e]: average exposure		1.0, 1.4 (1.1–1.7), 1.6 (1.3–2.0), 1.6 (1.2–2.0), 1.7 (1.2–2.3) (model likelihood 22.6, 4 d.f.)

[a] Units are mg/m^3-years for untransformed exposure, ln(mg/m^3-years $+1$) for logged exposure.

[b] Heterogeneity across studies was assessed by a test comparing the log likelihoods for the model with 10 interaction terms versus the model without these terms.

[c] Categories are quintiles of the cumulative exposure of the cases in the 10 studies, <0.4, 0.4–2.0, 2.0–5.4, 5.4–12.8, and $12.8+$ mg/m^3-years (median last category 28.0 mg/m^3-years).

[d] Units are mg/m^3 respirable silica.

[e] Categories are quintiles of the average exposure of the cases, <0.07, 0.07–0.21, 0.21–0.41, 0.41–1.36, >1.36 mg/m^3 (median last category, 3.75 mg/m^3).

not ($p = 0.08$, $p = 0.34$). Furthermore, no single interaction term between the log of exposure (15-year lag) and study was statistically significant at the 0.05 level; the closest was the interaction term for the South African study which had a p-value of 0.07. We ran the pooled analyses without the South Africa study; results were virtually unchanged. The coefficient for the log of cumulative exposure lagged 15 years was reduced from 0.062 (se 0.015) to 0.060 (se 0.015). Categorical analyses were likewise little changed. Therefore hereafter we refer only to analyses with all 10 studies included.

Models with simple duration of exposure (model likelihood 0.2, 1 d.f.) or log duration of exposure (model likelihood 0.5, 1 d.f.) did not fit the data well, indicating the importance of incorporating intensity of exposure into the exposure metric.

The model with the log of cumulative exposure lagged 15 years yielded a similar exposure–response coefficient for miners (0.050) and nonminers (0.077) (0.047 without the South African gold miners, where radon confounding may have been an issue); a test of heterogeneity between mines and nonmines showed little evidence of heterogeneity ($p = 0.36$). Categorical analyses by quintile of cumulative exposure of the cases (see footnote to Table 4) showed odds ratios of 1.0, 0.90 (0.66–1.2), 0.81 (0.59–1.1), 1.2 (0.89–1.6), and 1.4 (1.0–1.9) for mines and 1.0, 1.2 (0.92–1.6), 2.1 (1.6–2.8), 1.7 (1.2–2.4), and 1.5 (0.97–2.4) for nonmines. Exclusion of the three Chinese studies, under the premise of potential confounding by other lung carcinogens in these studies (see Methods), likewise did not appreciably change the results for the model using log of cumulative exposure lagged 15 years (the coefficient without the three Chinese studies was 0.075, se 0.025, $p = 0.003$).

A spline model (Figure 1) for the log of cumulative exposure with a 15-year lag showed an improvement over the model for log of cumulative exposure with a 15-year lag (change in log-likelihood 8.4, 3 d.f., $p = 0.04$). The spline model is relatively unconstrained, allowing any cubic curve between knots. The spline curve exhibits a reasonably monotonic increase in risk with increasing cumulative exposure.

We also fit a log-linear model for cumulative exposure (lagged 15 years) via a piece-wise regression (two linear pieces), using an iterative process to find the best cutpoint for a changing slope. The led to a good-fitting model (model likelihood 29.8, 2 d.f.) in which the slope was markedly upward (coefficient 0.146, se 0.046) until a cutpoint of 2.2 mg/m^3-years, and then decreased notably to a virtually flat slope (coefficient 0.008, se 0.002). However, marked heterogeneity between studies was noted for the piece-wise linear model. We also fit a

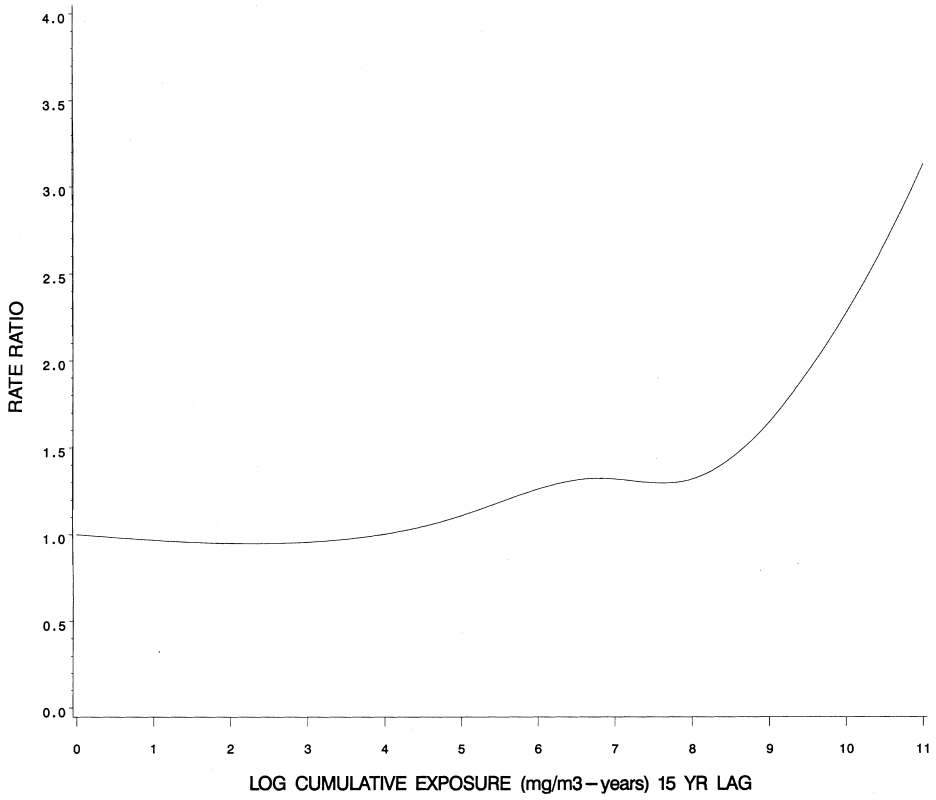

Fig. 1. Spline curve: log lung cancer rate ratio *vs.* log cumulative exposure 15-year lag.

piecewise linear model which assumed a threshold, *i.e.* no increase in risk up to a certain point (we considered three possible thresholds: 0.27, 0.54, 0.82 mg/m^3-years). These models did not fit as well as models in which risk increased continuously with increasing exposure.

Finally, we fit a series of linear models ($RR = 1 + \beta X$) which tended to fit about the same as the log-linear models. The pattern of heterogeneity was also similar, with marked heterogeneity unless the log of cumulative exposure was used.

We considered whether the case–control data for the English pottery workers [7] appeared compatible with results of the pooled analysis. In an analysis of the English data with smoking in the model the coefficient for the log cumulative exposure lagged 10 years was 0.11 ($p = 0.45$), and the coefficient for the log of cumulative exposure lagged 20 years was 0.08 ($p = 0.59$). These coefficients are of similar magnitude to our own estimate of 0.06 for log cumulative exposure lagged 15 years.

Using the spline model (with a 15-year lag), we estimated the excess lifetime (through age 75) risk of lung cancer death for a worker in China, the US, or Finland exposed to 0.10 mg/m^3 of respirable crystalline silica for 45 years (age 20–65), resulting in a cumulative exposure of 3.0 mg/m^3 by age 65. The excess (above background) lifetime risks were 1.1% (95% CI 0.1%, 2.3%), 1.7% (95% CI 0.2%, 3.6%), and 1.3% (95% CI 0.1%, 2.9%), respectively. Differences are due to differing background lung cancer rates and background all-cause death rates. The background lifetime risk of dying of lung cancer by age 75 in these countries is 3–6%. If one assumes that exposure is 0.02 mg/m^3 for 45 years, the lifetime excess risk ranges from 0.5 to 0.8; for an exposure of 0.01 mg/m^3 the lifetime excess ranges from 0.2% to 0.3%. Use of results from the model using the log of cumulative exposure (15-year lag) were slightly higher, showing a lifetime excess risk at an exposure of 0.10 mg/m^3 ranging from 1.7% to 2.8%, because of the steeper rise of the log curve versus the spline curve at lower cumulative exposures.

Discussion

This analysis represents the largest existing body of data for determining an exposure–response analysis for silica and lung cancer, with more than 1000 lung cancer cases.

We found a positive monotonic exposure–response trend across quintiles of cumulative exposure. There was a positive exposure–response trend using the log of

cumulative exposure, which was consistent across studies. A spline model, which does not impose a shape on the exposure–response curve, supported our other results.

As noted in Methods, we did not include three studies (Dutch ceramic cohort [5], second South Africa gold cohort [6], English pottery case–control [7]) which potentially or actually had information on quantitative exposure–response, due to confidentiality issues, data availability, or incompatibility. However, had these studies been included we believe they would not have changed our results appreciably. Published analyses of the Dutch ceramic cohort [5] (30 lung cancers) and the second South Africa gold miner cohort [6] (130 lung cancers) both showed a slight but positive exposure–response. As noted above, the English pottery cohort [7] gave results similar to our own when analyzed with log cumulative exposure and smoking in the model.

Our exposure–response coefficient from the pooled analysis is a weighted average of the exposure–response coefficient for each study. When we used the log of cumulative exposure lagged 15 years there were no significant interactions (at the 0.05 level) between study and exposure for any of the 10 studies. This did not mean that all 10 studies showed a strong positive exposure–response using the log of cumulative exposure, as can be seen from Table 3. Nonetheless, neither the study with the lowest nor highest exposure–response showed statistically significant outliers (at the 0.05 level) from the common estimated exposure–response for all 10 cohorts. Exposure data for occupational cohorts are usually log-normally distributed, with long tails to the right. Use of the log transformation tends to diminish the influence of the highest exposed individuals in each cohort on the exposure–response curve.

The fact that the log of cumulative exposure provided a good fit to the data with little heterogeneity across studies, implies that the relative risk of lung cancer due to silica exposure tends to tail off at the highest doses. There are a number of possible reasons for this, including biological saturation of the system after a certain degree of exposure, poor estimation of exposure at the highest intensities, the healthy worker survivor effect, and limits to the size of relative risk at high doses when the background rate of disease is high (depletion of susceptibles). Similarly diminished risks at the very highest exposure have been observed for a number of occupational carcinogens, including cadmium [44], radon [45], diesel [46], arsenic [47], and dioxin [48].

The majority of studies included in our analysis did not have data on smoking. This is an important concern in studies comparing exposed workers to a nonexposed general population, where increased smoking by workers can produce increases in lung cancer rate ratios on the order of 20–40% [49]. However, it is less of a concern in exposure–response analyses in which workers with high exposure are being compared to workers with low exposure, both groups presumably sharing similar smoking habits. We do not believe that confounding by smoking is likely to account for our results. In those studies where complete or partial smoking data were collected and considered in exposure–response analyses, either little confounding of exposure–response trends was observed (South Africa [21] and Australian gold miners [15], diatomaceous earth workers [17], Finnish granite workers [12]), or smoking was actually a negative confounder (English pottery workers [7]).

Another concern is confounding by other occupational carcinogens. This would be a particular concern in underground mines, where radon might be a confounder. However, the exposure–response trend was similar in mines and nonmines.

We did not have data on silicosis morbidity in most cohorts, and therefore did not attempt to analyze the effect of silicosis on lung cancer risk, independent of silica exposure level, an area of debate in the literature [50]. There has also been debate regarding whether the risk of lung cancer might be higher for cristobalite versus quartz [1]. Only one of our cohorts was primarily exposed to cristobalite (the diatomaceous earth cohort). The exposure–response trend within this cohort did not differ notably from trends in the remaining cohorts. Nonetheless, we suspect that other physical differences in silica between cohorts (e.g. freshness of particle cleavage, degree of coating with dust [8, 9]) may be a partial explanation of observed differences between studies.

Misclassification or mismeasurement of exposure was probably present in our study due to the lack of detailed and individual historical data on exposure. However, such misclassification or mismeasurement is unlikely to account for the positive exposure–response observed here. If there were no true positive exposure–response trend, nondifferential (with respect to outcome) and random misclassification or mismeasurement of exposure would be very unlikely to produce an apparent positive trend in either our categorical or continuous analyses [51–54].

Silica appears to a weaker carcinogen than other lung carcinogens measured by mass in the air. Figure 2 shows data for silica and for four other lung carcinogens which were measured in the same units (mg/m^3-years) of cumulative exposure, based on the midpoints of categorical data in four published studies [44, 55–57]. Silica appears the weakest of the five, with lower relative risks and a lower slope of the exposure–response curve.

Despite this relatively shallow exposure–response trend, overall our results tend to support the recent

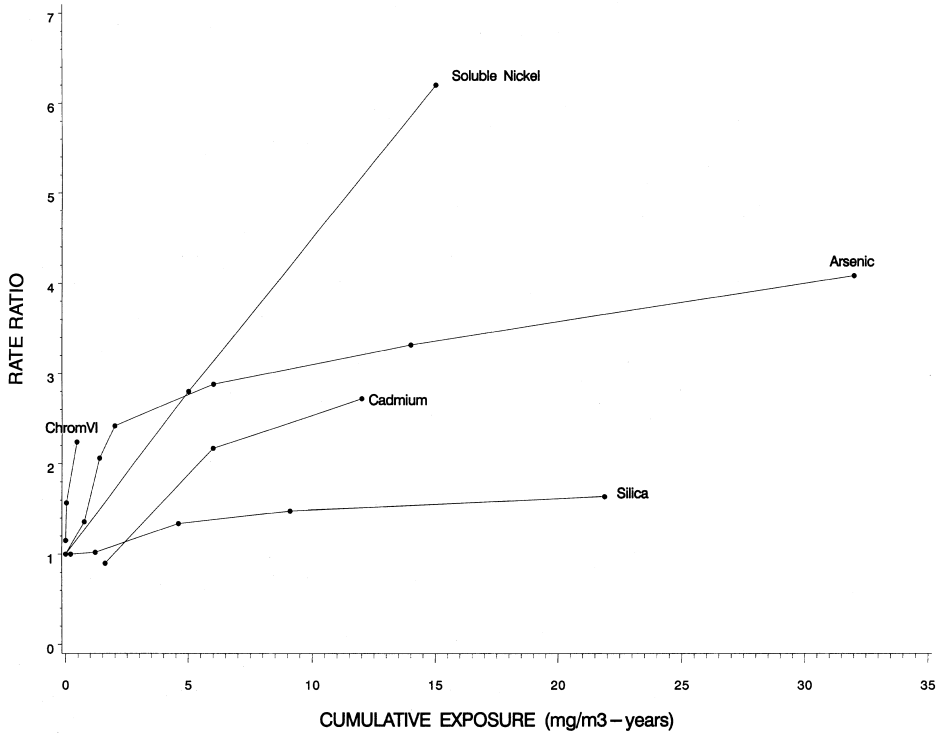

Fig. 2. Lung cancer rate ratios *vs.* cumulative exposure comparing five agents.

conclusion by the IARC [1] that inhaled crystalline silica in occupational settings is a human carcinogen, and suggest that existing permissible exposure limits for silica need to be lowered.

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